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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/442,542	11/18/1999	LONNIE D SHEA	30275/40877	6026

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/442,542	SHEA ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-18,48,54-65,106-108 and 118-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-18,48,54-65,106-108 and 118-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/9/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 4/11/05 has been acknowledged.

Claims 14-18, 48, 54-65, 106-108, 118-130 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Double Patenting

Claims *14-18, 48, 54-65, 106-108 and 118-130 stand* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-53 of U.S. Pat. No. 6,642,363 in view of claims 1-35 of U.S. Pat. No. 6797738, claims 1-36 of U.S. Pat No. 6281256, claims 1-77 of US 5763416 and claims 1-130 of U.S. Pat. No. 594296 for the same reasons of record as set forth in the office action mailed on 01/07/05

The claims of pending U.S. App. No. 09442542 are drawn to a composition comprising a porous modified alginate matrix that comprises at least one alginate chain section bonded to at least one molecule that mediates cellular interaction (i.e. RGD) and a nucleic acid segment in non-covalent association with the matrix.

The claims of USPN 6,642,363 are drawn to a modified alginate matrix comprising at least one alginate chain section, which is covalently bonded to at least one cell attachment polypeptide or RGD-polypeptide, which promotes cell adhesion and growth. However the '363 does not claim a modified alginate matrix, which is in the form of porous matrix and contains nucleic acid molecules.

The claims of USPN 6797738 and 6281256 are drawn to a porous polymer alginate material, wherein the pores are formed by gas foaming (CO_2) and leaching out the particulate material (NaCl). The claims are further drawn to the polymer material comprising a drug and/or viable cells contained within the pores of porous polymer.

The claims of USPN 5763416 and 5942496 are drawn to a composition comprising one or more nucleic acid segments in association with structural bone-compatible matrix. The claims are further drawn to a matrix composition that contains one or more genes selected from parathyroid hormone (PTH: PTH1-34) gene, a bone morphogenetic protein gene (BMP: BMP-2A, BMP-2B, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 or BMP-8 gene), a growth factor gene, a growth factor receptor gene, a cytokine gene or a chemotactic factor gene, transforming growth factor (TGF) gene, a fibroblast growth factor (FGF) gene, a granulocyte/macrophage colony stimulating factor (GMCSF) gene, an epidermal growth factor (EGF) gene, a platelet derived growth factor (PDGF) gene, an insulin-like growth factor (IGF) gene, a latent TGF-.beta. binding protein (LTBP) gene or a leukemia inhibitory factor (LIF) gene.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the RGD-linked alginate matrix of USPN 6,642,363 by introducing a pore structure in view of USPN 6797738 and 6281256 using gas foaming and/or particulate leaching. One would have been motivated to introduce porous structure in the matrix to contain drugs or viable cells in order to make a drug delivery system. It would have been further obvious to one ordinary skill in the art to substitute a drug with a nucleic acid molecule in view of USPN 5763416 and 5942496 which teaches a method of transferring nucleic acid segments into viable cells of an animal by contacting a matrix structure containing one or more nucleic acid of interest. One would have been motivated to do so to genetically modify the cells in order to produce recombinant proteins of interest. One would have a reasonable expectation in doing so, since modification of alginate chains to include a molecule of interest and making a porous structure by gas foaming and particulate leaching was routine in the art at the time the instant invention was made. In addition one would have a reasonable expectation of success in making and using a porous alginate matrix containing nucleic acid because

such a composition had been well within the reach of one ordinary skilled in the art at the time the instant invention was made. Thus the invention as claimed is an obvious variation over cited patents of record.

Response to Arguments

Applicant's arguments filed on pages 6-7 regarding double patenting issues have been fully considered but they are not persuasive. The applicant argues that none of the claims in the '416 patent, the '496 patent, the '738 patent or the '256 patent recite an alginate matrix expressly claimed in the instant application. Accordingly, the claims of these patents, alone or in combination, cannot render obvious the subject matter of the instant application. The applicant argues that the only claims in the '363 patent set forth an alginate product. On the contrary the applicant argues that it is unclear as to how much term the applicants are requested to disclaim should a *terminal disclaimer* be filed.

However, applicant's argumetns are found not persuasive. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In instant case the claim of '363 are drawn to a modified alginate matrix comprising at least one alginate chain section, which is covalently bonded to at least one cell attachment polypeptide or RGD-polypeptide, which promotes cell adhesion and growth. The claims of '738 and '256 are drawn to a porous polymer alginate material. The claims of '416 and '496 are drawn to a composition comprising one or more nucleic acid segments in association with structural bone-compatible matrix. As stated above the combined teaching of earlier patents clearly makes the instant invention prima facie obvious.

Regarding the filing a proper terminal disclaim applicant's attention is drawn to MPEP § 804.02 and MPEP §1490.

Claim Rejections - 35 USC § 103

Claims 14, 17, 18, 48, 106-108 and 118-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al (Biomaterials 18:583-590, 1997) in view of Fang et al (PNAS 03:5773-5758, 1996) and Kawada et al (FEBS Letts. 408;43-46, 1997), for the same reasons of record as set forth in the office action mailed on 01/07/05

The scope of instant claim encompasses a porous alginate matrix that comprises a molecule bound to alginate chain that mediates cellular interaction and a nucleic acid segment in a non-covalent association with the porous alginate matrix.

Shapiro teaches a porous alginate sponges for the cell culture and transplantation. The cited art teaches the making of cross-link alginate sponges that contains porous structures (page 584, col.1, para.3-4). The cited art further teaches investigation by electron microscopy reveled that the pore size can be controlled by variation in alginate and cross-linker concentration (page 586, table-2, fig-3). The cited art further teaches tissue cell culture in alginate sponges (page 585, col.1 para. 2). Even though the cited art teaches a porous alginate matrix the cited art does not teach incorporation of nucleic acid molecules in the matrix and that the matrix is capable of mediating cellular interaction via alginate chain section.

Fang teaches gene-activated matrices (GAMs) comprising a biodegradable matrix containing nucleic acid molecules. The cited art teaches the preparation of collagen sponges that contains plasmid DNA molecules (page 5753 abstract, page 5754, col.2). Regarding claims 125, 106-108 the cited art teaches the transplantation of gene-activated matrices in an animal model that resulted in the expression of a marker gene, PTH-34, BMP-4 or TGF-b genes in host animals (page 5755, fig-2, page 5756, fig-4, page 5757, fig-5). The cited art further teaches that implantation of porous matrices (sponges) containing the nucleic acid molecules results in the genetic modification of host cells that in turn produces the gene product of interest (page 5756 fig-4; page 5757 col.2 para.2). Regarding claims 118-121 the cited art teaches that the nucleic acid incorporated in the matrix encompasses plasmid expression vectors

encoding PTH-34, BMP-4 genes, which stimulates bone progenitor cells. Regarding claims 122-124 the cited art teaches that nucleic acid of interest encompasses marker genes, PTH-34, BMP-4 and TGF-b genes that are capable of modulating fibroblast growth and immune response. Regarding claims 126-130 the cited art teaches that plurality of nucleic acid segments can be introduced in gene-activated matrices which transfeccts host cells at the site of transplantation. For example the cited art teaches transfer and expression of plasmid mixture (BMP-4 + PTH1-34) in host animals using gene-activated matrices (page 5756, col.2 para.2).

Kawada teaches alginate contains mixture of oligosaccharides that are capable of mediating cellular interaction (see abstract). The cited art further teaches isolation of alginate oligosaccharide having proliferative activity (page 45 col.1). For example the cited art teaches that alginate oligosaccharides showing proliferative effects have gulonic acid in the reduced terminus (page 45 col.2, fig-4). Regarding claim 14 specifically the cited art teaches that alginate derived oligosaccharides included –4)-O-a-D-mannopyranuronic acid residues (page 45 col.1 para 3).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Shapiro who teaches a porous alginate sponges by incorporating nucleic acid molecules as taught by Fang. One would have been motivated to do so to induce gene expression of interest in host cells at the site of sponge transplantation. One would have a reasonable expectation of success in doing so, since genetic modification of host cells by transplanting a porous matrix has been routine in the art at time the instant invention was made. In addition given the scope of a molecule that mediates a cellular interaction the alginate matrix inherently contains alginate chains section bonded to various oligosaccharides that mediates cellular interaction (see Kawada). Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to Arguments

Applicant's arguments filed on pages 8-11 regarding prior art issues have been fully considered but they are not persuasive. The applicant argues that there is no motivation to combine the teaching of Shapiro with Fang. The applicant argues that the

use of mammalian matrix e.g. collagen as taught by Fang would be rather a desirable choice over alginate matrix. The applicant argues that the alignate is not a desirable choice, since kinetics of alginate matrix degradation in vivo remains to be elucidated. The applicant argues that therefore one would not be motivated to substitute alginate for Fang's collagen matrix.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (See MPEP 2144).

In this case, Shapiro clearly teaches the successful use of a porous alginate sponges for the cell culture and transplantation. Furthermore Fang clearly provides motivation to incorporate nucleic acid molecules in the alginate sponge as taught by Shapiro in order to transduce cells. Furthermore one would have been motivated to do so to induce gene expression of interest in host cells at the site of sponge transplantation. In addition one would have a reasonable expectation of success in doing so, since genetic modification of host cells by transplanting a porous matrix has been routine in the art at time the instant invention was made. In addition given the scope of a molecule that mediates a cellular interaction the alginate matrix inherently contains alginate chains section bonded to various oligosaccharides that mediates cellular interaction (see Kawada). The phrase "mediating cellular interaction via alginate chain section [action p.5] refers to "matrix is capable of mediating cellular interaction via alginate chain section" in view of limitation recited in claim 14. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

Sumesh Kaushal
Examiner GAU 1633

SUMESH KAUSHAL
PATENT EXAMINER